

REMARKS

Claims 32-33, 38, 41-47, 49-63 constitute the pending claims in the present application. Claims 32-33, 38, 41-47, 49-60 were elected with traverse. Applicants cancel, without prejudice, non-elected claims 61-63. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants acknowledge with appreciation that the finality of the previous Office Action has been withdrawn, and that the submission filed 7/11/01 has been entered.
2. Applicants note that claims 61-63 are directed to a non-elected invention, and are withdrawn from consideration. Claims 32-33, 38, 41-47, 49-60 are currently under consideration. Applicants cancel, without prejudice, claims 61-63.
3. Applicants note with appreciation that the rejection of claim 38 as being anticipated by Sosnowski et al., in light of Fraichard et al., has been withdrawn. Applicants further note that the rejection of claim 33 as unpatentable over Mayo et al., in view of Kaufman et al., has been withdrawn.
4. Claims 32-33, 38, 41-47, and 49 are rejected under 35 U.S.C. 101 for allegedly being directed to non-statutory subject matter. Specifically, claim 49 is allegedly directed to naturally occurring stem cells. To expedite prosecution, Applicants have amended claim 49 to explicitly point out the characteristics of the claimed stem cells. Such an amendment is not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of the rejection is requested.
5. Claims 32-33, 38, 41-47, 49-63 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, specifically for being overly broad in the recitation of "stem

cells." The Examiner has suggested that the application is enabling for a "neural" stem cell. Applicants respectfully traverse this rejection.

Applicants characterize their invention as relating to "multipotential precursor cells isolated from peripheral tissues containing sensory receptors such as the olfactory epithelium and tongue" (page 1, lines 8-9). Although the examples presented in this application detail the differentiation of these cells to neuronal cell types including oligodendrocytes, astrocytes, and neurons, the cells of the invention may be able to differentiate to additional cell types. Applicants contention that the multipotential cells of the invention may differentiate along non-neuronal fates, and thus can reasonably be referred to generally as stem cells, is supported by the results obtained from experiments with other stem cell populations. Pereira et al. summarize the work carried out by many investigators demonstrating that "marrow contains mesenchymal precursor cells that produce fibrous tissues, bone, or cartilage when implanted into appropriate tissues *in vivo* and that generate colonies of fibroblastic, adipocytic, and osteogenic cells when cultured under appropriate conditions (Pereira et al., 1995, page 4857, column 1, enclosed herewith as Exhibit 1). Pereira et al. further underscores the effect of culture conditions on the fate of cells derived from stem cells. "If the adherent cells are cultured in the presence of hydrocortisone or other selective conditions, populations enriched for hematopoietic precursors or osteogenic cells are obtained. If cultured for ~ 1 week under the conditions employed here, the predominant cells in the cultures are fibroblast-like." (Pereira et al., 1995, page 4860, column 1). Petersen et al. further illustrates the effect of culture/environmental conditions on stem cell fate, and presents evidence that mesenchymal stem cells can differentiate along an epithelial lineage (Petersen et al., 1999, enclosed herewith as Exhibit 2).

Moreover, amending the claims to include any further recitation of the potential of the subject stem cells to give rise to neuronal cells is inconsequential to the scope of the claims. The cells are what they are, multipotent stem cells. Applicants have provided limitations in the claims which are already sufficient to distinguish these cells from the art and cover subject matter enabled by the disclosure. Therefore, classifying a stem cell as "neuronal" based solely on the cell's original location is not an accurate representation of the inherent state of that cell. Accordingly, Applicants submit that the term "stem cell" is an accurate description of the cells of the invention, and is not overly broad. Reconsideration and withdrawal of this rejection is respectfully requested.

6. Claims 49-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Avoli et al. Applicants traverse this rejection to the extent it is maintained over the amended claims.

Avoli et al. teach a method for measuring the spontaneous synchronous potentials using human brain slices. The prior office action concludes that the brain slices "can be considered purified cellular compositions, because they comprise many different types of cells, and are isolated from their *in vivo* milieu. These purified cellular compositions comprise cells that meet all the limitations set forth in claims 50-60, thus the claims are anticipated." However, Avoli et al. fail to describe a cellular composition of stem cells.

Claim 49 has been amended to explicitly point out that the stem cells are a cellular composition of stem cells. Applicants contend that such an amendment distinguishes the cells of the present invention from the cells taught by Avoli et al. Although the brain slices of Avoli et al. may contain stem cells, Avoli et al. fails to describe a cellular composition of these stem cells. Any stem cells present in the brain slices taught by Avoli et al. are found within the microarchitecture and vast array of other cell types contained within the brain slice, and have not been isolated from that environment as required by claim 49.

Furthermore, Applicants note that claims 49-53 are directed to stem cell compositions which form non-adherent cultures. The cells of Avoli et al. are present in the context of brain slices, and there is no evidence or reason to expect that cells within these brain slices can form non-adherent clusters.

Applicants remind the Examiner that in accordance with MPEP 2112, "[T]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." The cells taught by Avoli et al. fail to meet the limitations set forth in the claims. Accordingly, the cells of Avoli et al. do not anticipate the claimed subject matter. Reconsideration and withdrawal of this rejection is requested.

7. Claims 32, 38, 43-47, 49, 53-57, and 59-60 are rejected under 35 U.S.C. 102(a) as being anticipated by Sosnowski et al. as evidenced by Bruckenstein et al. Applicants traverse this rejection to the extent that it is maintained over the amended claims.

As pointed out by the Examiner in the prior office action, "at issue is whether the cell composition disclosed by Sosnowski et al. comprises cells which inherently meet the limitations

set forth in the indicated claims." Applicants have previously argued that the claimed cells can be readily distinguished from the cells of Sosnowski et al. based on the tendency of the claimed cells to proliferate as non-adherent clusters. That argument is maintained for purposes of rebutting the outstanding rejection. Furthermore, Applicants point out that such dramatically different morphological properties suggest differences in cellular properties which allow the cells to proliferate as non-adherent clusters, including differential expression of adhesion molecules.

The Examiner argues that the claimed cells are inherently the same cells as the cells taught by Sosnowski et al., and that the difference in cellular characteristics between the two cell types are the result of differing culture conditions. The Examiner further cites Bruckenstein et al. to support the contention that differing culture conditions may affect the morphology of cells. As above, Applicants remind the Examiner that in accordance with MPEP 2112, "[T]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic."

"*In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities (emphasis added). The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-1951 (Fed Cir. 1999) (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fasterning element, either expressly or inherently.)"

MPEP 2112

For the reasons already of record, Applicants maintain that the cells taught by Sosnowski et al. fail to meet the limitations set forth in the claims. Furthermore, the teachings of Bruckenstein et al. do not overcome the deficiencies of Sosnowski et al. Bruckenstein et al. teach that differences in plating conditions can affect the morphology of neurons. Bruckenstein et al. fail to demonstrate that such plating conditions necessarily alter neuronal morphology. Additionally, the experiments of Bruckenstein et al. are performed on neuronal cultures, and the

effects on cellular morphology are demonstrated for differentiated neurons. No experiments are performed to address the effects of plating conditions on stem or progenitor cells, either in an undifferentiated or a differentiated state. Accordingly, Applicants submit that the cells of the present invention are not anticipated by Sosnowski et al., in light of Bruckenstein et al.

Finally, Applicants point out that the mere fact that the cells of Sosnowski et al. are isolated from the same region of the animal (the olfactory epithelium) is not evidence that the cells are inherently the same cells. The heterogeneous nature of the cultures described in Sosnowski et al. demonstrate that the olfactory epithelium consists of a wide range of cell types (page 45, second column, as cited by the Examiner). Additionally, it was evident at the time the present invention was made that specific tissues contain not only distinct cell types, but also distinct types of stem cells. For example, bone marrow was known to contain both mesenchymal stem cells and hematopoietic stem cells. These two stem cell populations are distinct not only in morphology, but also in marker expression.

Applicants maintain that the cells of the present invention are not anticipated by the teachings of Sosnowski et al. The cells of Sosnowski et al. fail to meet the limitations set forth in the claims, and these limitations are not overcome by the teachings of Bruckenstein et al. Accordingly, reconsideration and withdrawal of this rejection is requested.

8. Claims 33 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Mayo et al. Applicants submit that the amendment to claim 49 specifying that the stem cells are a cellular composition of stem cells obviates the rejection. Mayo et al. teaches progenitor cells in the context of tongue explants. Mayo et al. does not provide a cellular composition of progenitor cells isolated from the context of the various other cell types and cytoarchitecture of the tissue explant. Accordingly, Applicants contend that Mayo et al. fail to meet the limitations set forth in the claims, and therefore amended claim 49 and dependent claim 33 are not anticipated by Mayo et al. Reconsideration and withdrawal of this rejection is requested.

9. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sosnowski et al. in view of LaSalle et al. Applicants maintain that the claimed cells are distinct from the cells taught by Sosnowski et al., as outlined in detail in section 7 above. LaSalle et al. demonstrate that primary neuronal cultures can be transfected with a heterologous gene using an

adenoviral vector. LaSalle et al. do not demonstrate that such a system can be used to transfect the cells taught by Sosnowski et al., nor any stem cell or progenitor cell taught in the prior art. Accordingly Applicants submit that the teachings of LaSalle et al. do not overcome the deficiencies of Sosnowski et al. Reconsideration and withdrawal of this rejection are requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 18-1945.

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